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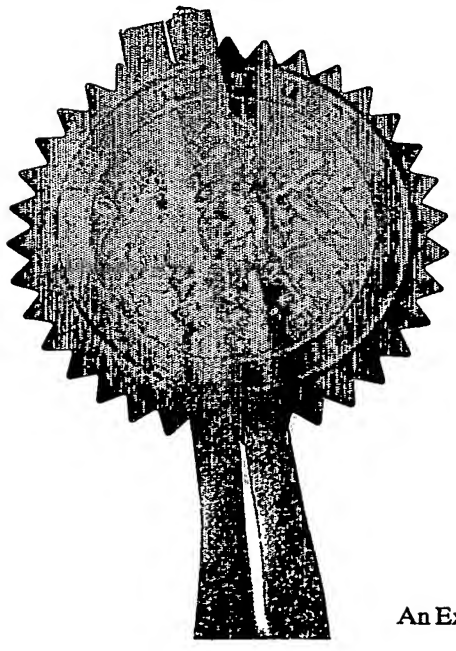

Signed P. Mahoney

Dated 17 April 2003

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P01/7700 0.00-0222177.8

Patents Form 1/77

THE PATENT OFFICE
24 SEP 2002

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The **Patent Office**

1/77

Request for grant of a patent

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1.	Your reference	**G-32500P2/ABR 9919**	
2.	Patent application number *(The Patent Office will fill in this part)*	0222177.8	24 SEP 2002
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	**BIOCHEMIE GESELLSCHAFT MBH** **A-6250 KUNDL/TIROL** **AUSTRIA**	
	Patent ADP number *(if you know it)* If the applicant is a corporate body, give the country/state of its incorporation	**AUSTRIA**	8355158001
4.	Title of invention	**Organic compounds**	
5.	Name of your agent *(If you have one)* "Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	**B.A. YORKE & CO.** **CHARTERED PATENT AGENTS** **COOMB HOUSE, 7 ST. JOHN'S ROAD** **ISLEWORTH** **MIDDLESEX TW7 6NH**	
	Patents ADP number *(if you know it)*	**1800001**	

6.	If you are declaring priority from one ore more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country	Priority application number *(if you know it)*	Date of filing (day/month/year)
7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application		Number of earlier application	Date of filing (day/month/year)
8.	Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:* *a) any applicant named in part 3 is not an inventor, or* *b) there is an inventor who is not named as an applicant, or* *c) any named applicant is a corporate body.* *(see note (d))*	**Yes**		

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Description	29 ✓
Claim(s)	2 ✓
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Drawing(s)	

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Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	ONE ✓
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application

Signature B. A. Yorke & Co. Date

B.A. Yorke & Co. 24 September 2002

12. Name and daytime telephone number of person to contact in the United Kingdom

Mrs. E. Cheetham
020 8560 5847

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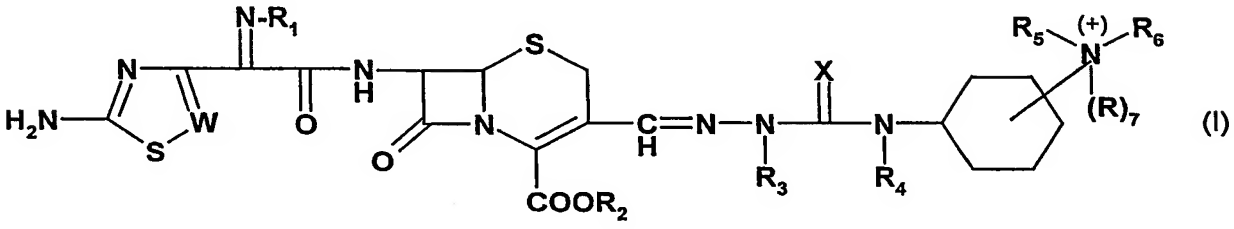
Organic compounds

The present invention relates to organic compoundse.g. antimicrobial compounds such as cephalosporines.

In one aspect the present invention provides a compound of formula



(I)

wherein

W is CH or N,

R_1 is hydrogen, hydroxy, (C_{1-6})alkoxy, halo(C_{1-6})alkoxy, hydroxycarbonyl(C_{1-6})alkoxy or (C_{1-6})alkyloxycarbonyl(C_{1-6})alkoxy,

R_2 is hydrogen or an ester moiety,

R_3 is hydrogen, (C_{1-6})alkyl, allyl or cyclo(C_{1-6})alkyl,

R_4 is hydrogen or methyl,

R_5, R_6 and R_7 are independently from each other hydrogen, (C_{1-6})alkyl, (C_{1-6})alkylcarbonyl, arylcarbonyl, aryl(C_{1-6})alkycarbonyl, heteroaryl(C_{1-6})alkylcarbonyl, (C_{1-6})alkylsulfonyl, arylsulfonyl or aryl(C_{1-6})alkylsulfonyl, or R_7 is missing and N^+-$R_5R_6R_7$ or N-R_5R_6 can be in o, m or p position, and

X is N-R_8 , O, S, O-R_8 or S-R_8 wherein R_8 is hydrogen, (C_{1-6})alkyl, cyclo(C_{1-6})alkyl or aminocyclo(C_{1-6})alkyl.

In a preferred aspect the present invention provides a compound of formula I wherein

W is CH or N,

R_1 is hydroxy, methoxy, fluoromethoxy, hydroxycarbonylmethoxy or hydroxycarbonylisopropyloxy,

R_2 is hydrogen,

R_3 is hydrogen, methyl, allyl or cyclopropyl,

R_4 is hydrogen or methyl,

R_5, R_6 and R_7 are independently from each other hydrogen, methyl, phenylcarbonyl, aryl substituted by acetyloxo, phenyloxyacetyl, phenylsulfonyl substituted by amino or acetylamino, 1-thiophene-2-yl-acetyl or cyclohexyl substituted by amino, or R_7 is missing and N^+-$R_5R_6R_7$ or N-R_5R_6 can be in o, m or p position, and

X is NH, NCH_3, O, S, S-(C_{1-6})alkyl, amino substituted aminocyclohexyl.

An ester moiety includes alkyl; e.g. unsubstituted alkyl or substituted alkyl, e.g. by aryl, such as benzyl, alkoxybenzyl, such as 4-methoxybenzyl, alkoxy, such as methoxymethyl; alkyloxycarbonyloxy; alkyl; alkoxy, such as glycyloxy, phenylglycyloxy, e.g. glycyloxymethyl, phenylglycyloxymethyl; heterocyclyl e.g. 5-methyl-2-oxo-1,3-dioxolen-4-yl; indanyl, phthalidyl, alkoxycarbonyloxy and ester moieties which form with the COO^- group a physiologically hydrolysable and acceptable ester, *e.g.* such known to be hydrolysable ester groups in the field of cephalosporins. A compound of formula I may thus be in the form of an physiologically-hydrolysable and -acceptable ester. By physiologically-hydrolysable and -acceptable esters as used herein is meant an ester in which the COO- group is esterified and which is hydrolysable under physiological conditions to yield an acid which is itself physiologically tolerable at dosages to be administered. The term is thus to be understood as defining regular pro-drug forms. An ester moiety may be preferably a group which is easily hydrolysable under physiological conditions. Such esters may be administered preferably orally. Parenteral administration may be indicated if the ester *per se* is an active compound or, if hydrolysis occurs in the blood.

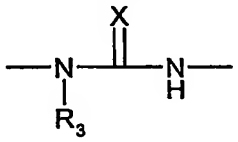
If not otherwise indicated herein any carbon containing group may contain up to 20 carbon atoms, *e.g.* alkyl includes, e.g. straight chain and branched, (C_{1-20}), *e.g.* (C_{1-8})alkyl, such as (C_{1-6})alkyl and lower alkyl. Lower alkyl includes *e.g.* (C_{1-4})alkyl, such as (C_{1-2})alkyl. Alkenyl includes C_{2-20} , e.g. C_{2-20}. Lower alkenyl includes e.g. C_{3-6}alkenyl , preferably C_3alkenyl. Cycloalkyl includes, for example (C_{3-7})cycloalkyl, such as C_3, C_5 or C_6 cycloalkyl. Acyl includes alkylcarbonyl and arylcarbonyl, e.g. (C_{1-12})acyl, *e.g.* (C_{1-6})acyl, such as (C_{1-4})acyl. Aryl includes (C_{6-18})aryl, preferably phenyl, naphthyl, e.g. phenyl.

Any group(s) may be unsubstituted or one or morefold substituted, e.g. substituted by hydroxy, (C_{1-4})alkoxy, (C_{1-4})haloalkoxy, hydroxycarbonyl(C_{1-4})alkoxy, alkylcarbonyl(C_{1-4})alkoxy, allyl or cyclo(C_{1-4})alkyl.

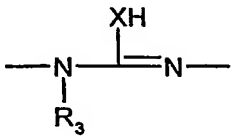
In this specification unless otherwise indicated terms such as "compound of formula I" embrace the compound in any form, for example in the form of a salt and in free base form. The present invention thus includes a compound in free base form or, e.g. where such forms exist, in the form of a salt, for example in the form of an acid addition salt, inner salt, quaternary salt and/or in the form of a solvate, for example in the form of a hydrate. A salt may be a pharmaceutically acceptable salt of a compound of formula I such as a metal salt or an amine salt. Metal salts include for example sodium, potassium, calcium, barium, zinc, aluminum salts, preferably sodium or potassium salts. Amine salts include for example trialkylamine, procaine, dibenzylamine and benzylamine salts. A free form of a compound of formula I may be converted into a salt form and *vice versa*.

In a further aspect the present invention provides a compound of formula I in free form and in the form of a salt, for example an acid addition salt or a metal salt; and a compound of formula I, e.g. in free form, in the form of a salt, in the form of a solvate or in the form of a salt and a solvate. For example R_2 may be the cation of a pharmaceutically acceptable salt forming agent.

The present invention includes a compound of formula I in any isomeric/tautomeric from in which it may exist. E.g. the configuration in group



may (co)exist in the form of



Also e.g. geometric isomers if R_1 is other than hydrogen may be syn [(Z)] and anti [(E)] and is preferably syn [(Z)]. E.g. a chiral carbon atom may be introduced, e.g. during a production process of a compound of formula I and corresponding stereoisomeric forms of a compound of formula I may be obtained, e.g a mixture of the individual stereoisomers, e.g. a racemate, or pure isostereoisomeric forms. Mixtures of isomers may be separated.
The present invention includes a compound of formula I in any tautomeric form, in any isomeric mixtures and in the form of pure isomers.

Any compound mentioned herein, e.g. a compound of the present invention, may be prepared as appropriate, e.g. analogously to a method as conventional or as disclosed herein.

In another aspect the present invention provides a process for the production of a compound of formula I by reaction of a appropriate starting materials according to various reaction schemes as outlined below.
If desired, reactive groups may be protected with protecting groups, which may be, or, which are split off under the reaction conditions, or after the reaction. A compound of formula I wherein R_2 is hydrogen may be converted into a compound of formula I wherein R_2 is an carboxylic acid ester group. A compound of formula I may be isolated from the reaction mixture as approptiate, e.g. analogously to a method as conventional.

The compounds of formula I including salt/solvate, hereinafter designated as "active compound(s) of the invention" exhibit pharmacological activity, e.g. beside low toxicity and are therefore useful as pharmaceuticals. In particular, the active compounds of the invention show antimicrobial, *e.g.* antibacterial, activity against e.g. gram negative and gram positive bacteria, e.g. gram positive bacteria, such as *e.g.* Escherichia, e.g. Escherichia coli; Enterobacter, e.g. Enterobacter cloacae; Enterococcus, e.g. Enterococcus faecalis; Klebsiella, e.g. Klebsiella pneumoniae; Streptococcus, e.g. Streptococcus pneuminiae; Staphylococcus, e.g. Staphylococcus aureus; and Pseudomonas, e.g. Pseudomonas aeruginosa, in vitro in the Agar Dilution Test according to National Commitee for Clinical Laboratory Standards (NCCLS) 1993, Document M7-A3Vol.13, No. 25: "Methods for dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically - Third Edition, Approved Standard". The active compounds show an MIC (µg/ml) in the Agar Dilution Test from about <0.0125 to ca. >6.25. The active compounds of the invention show a surprising overall activity spectrum.

In another aspect the present invention provides an active compound for use as a pharmaceutical, preferably as an antimicrobial agent, such as an antibiotic.
In a further aspect the present invention provides an active compound of the present invention for use in the preparation of a medicament for the treatment of microbial diseases, for example diseases mediated by bacterias selected from *Escherichia, Enterobacter, Enterococcus, Klebsiella, Streptococcus, Staphylococcus and Pseudomonas.*

The present invention provides in further aspects

- an active compound of the present invention for use as a pharmaceutical in the treatment of microbial diseases caused by bacterias selected from Escherichia, Enterobacter, Enterococus, Klebsiella, Streptococcus, Staphylococcus and Pseudomonas;
- the use of an active compound of the present invention or the use of a pharmaceutical composition comprising an active compound of the present invention as a pharmaceutical and
- a method of treatment of microbial diseases which comprises administering to a subject in need of such treatment an effective amount of an active compound of the present invention.

Treatment includes disease treatment as well as prophylactic treatment.

In a further aspect the present invention provides a method of treatment of microbial diseases which comprises administering to a subject in need of such treatment an effective amount of an active compound of the present invention.

For this indication, the appropriate dosage will, of course, vary depending upon, for example, the compound of formula I used, the host, the mode of administration and the nature and severity of the conditions being treated. However, in general, for satisfactory results in larger mammals, for example humans, an indicated daily dosage is in the range from about 0.05 to 5 g, for example 0.1 to about 2.5 g, of an active compound of the invention conveniently administered, for example, in divided doses up to four times a day.

An active compound of the invention may be administered by any conventional route, for example orally, *e.g.* in form of tablets or capsules, or parenterally in the form of injectable solutions or suspensions, e.g. in analogous manner to ceftazidime.

The compound of example 1 is a preferred compound of the present invention.

It has, for example been determined that the MIC (µg/ml) of the compound of Example 1 against, for example Klebsiella pneumoniae is about 0.0125. It is therefore, indicated that for the treatment of microbial diseases, *e.g.* bacterial diseases, the preferred compounds of the invention may be administered to larger mammals, for example humans, by similar modes of administration at similar dosages than conventionally used with ceftazidime.

The compounds of formula I may be administered in pharmaceutically acceptable salt form, *e.g.* acid addition salt form or base addition salt form or in the corresponding free forms, optionally in solvate form. Such salts exhibit the same order of activity as the free forms.

In another aspect the present invention provides a pharmaceutical composition comprising an active compound of the present invention in association with at least one pharmaceutically excipient. Such compositions may be manufactured accordingly, e.g. analogously to a method as conventional. Pharmaceutical excipient(s) include(s) pharmaceutically active carrier and diluent.

In the following examples which illustrate the present invention all temperatures are given in degree centigrade. RT means room temperature.

EXAMPLES

Example 1:

A) SYNTHESIS OF INTERMEDIATE COMPOUNDS

a) Benzylidene derivative of 3-amino-1-(trans-4-aminocyclohexyl)-3-methyl-guanidine in the form of a monohydrochloride

35 g of the benzylidene derivative of S-methyl-2-methyl-isothiosemicarbazide in the form of a hydrochloride and 32.79 g trans-1,4-diaminocyclohexane in 300 ml methanol are refluxed. The mixture obtained is stirred at RT, a precipitate forms, is filtered off and solvent is evaporated. The evaporated residue is treated with 217.5 ml 2 M HCl, a precipitate formed is filtered off, washed and dried. The volume of the filtrate obtained is brought to about 150 ml, a precipitate is formed, filtered off, washed and dried. The dried, combined precipitates are recristallized from water and the benzylidene derivative of 3-amino-1-(trans-4-aminocyclo hexyl)-3-methyl-guanidine in the form of a monohydrochloride is obtained in form of a white solid.

b) 3-amino-1-(trans-4-aminocyclohexyl)-3-methyl-guanidine dihydrochloride

From a mixture of 24.74 g benzylidene derivative of 3-amino-1-(trans-4-aminocyclohexyl)-3-methyl-guanidine in the form of a monohydrochloride in 79.9 ml 2 M HCl, benzaldehyde is destilled off and solvent from the remaining mixture is evaporated. 3-Amino-1-(trans-4-aminocyclohexyl)-3-methyl-guanidine in the form of a dihydrochloride is obtained.

B) SYNTHESIS OF SUBSTITUTED CEPHALOSPORINES

a) 3-{(E)[[1-trans-(4-amino-cyclohexylamino)-iminomethyl]-methylhydrazono] methyl}-7-{[(5-amino-[1,2,4]thiadiazol-3-yl)-(Z)-(fluoromethoxyimino)-acetyl] amino}-3-cephem-4-carboxylic acid trihydrochloride

To a mixture of 2 g 3-amino-1-(trans-4-aminocyclohexyl)-3-methyl-guanidine in the form of a dihydrochloride in 3.4 ml 2 M HCl and 6.1 ml dimethylacetamide, 2.78 g of N-(1,4,5a,6-tetrahydro-3-hydroxy-1,7-dioxo-3H,7H-azeto(2,1-b)furo(3,4-d)(1,3)-thiazin-6-yl)-2-(5-amino-1,2,4-thiadiazol-3-yl)-(Z)-2-(fluoromethoxyimino) acetic acid amide are added and the suspension obtained is stirred at RT. The mixture obtained is poured into acetonitrile under stirring. A precipitate formed is filtrated off, washed and dried. 3-{(E)[[1-Trans-(4-amino-cyclohexylamino)-iminomethyl]-methylhydrazono]methyl}-7-{[(5-amino-1,2,4-thiadiazol-3-yl)-(Z)-(fluoromethoxyimino)-acetyl] amino}-cephem-4-carboxylic acid in the form of a trihydrochloride is obtained in the form of a yellow powder.

b) 3-{(E)[[1-trans-(4-amino-cyclohexylamino)-iminomethyl]-methylhydrazono] methyl}-7-{[(5-amino-1,2,4-thiadiazol-3-yl)-(Z)-(fluoromethoxyimino)-acetyl] amino}-3-cephem-4-carboxylic acid monohydrochloride

10 g of the crude 3-{(E)[[1-trans-(4-amino-cyclohexylamino)-iminomethyl]-methylhydrazono] methyl}-7-{[(5-amino-1,2,4-thiadiazol-3-yl)-(Z)-(fluoromethoxyimino)-acetyl] amino}-3-cephem-4-carboxylic acid in the form of a trihydrochloride are dissolved in 42 ml water, subjected to chromatography (e.g. LiChroprep RP-18^R, Merck, grain size 40-63 um) and eluated. Fractions containing the desired 3-{(E)[[1-trans-(4-amino-cyclohexylamino)-iminomethyl]-methylhydrazono]methyl}-7-{[(5-amino-1,2,4-thiadiazol-3-yl)-(Z)-(fluoromethoxyimino)-acetyl]amino}-3-cephem-4-carboxylic acid in the form of a monohydrochloride (HPLC determination) are combined and lyophilised. 3-{(E)[[1-Trans-(4-amino-cyclohexylamino)-iminomethyl]-methylhydrazono]methyl}-7-{[(5-amino-1,2,4-thiadiazol-3-yl)-(Z)-(fluoromethoxyimino)-acetyl]amino}-3-cephem-4-carboxylic acid in the form of a monohydrochloride is obtained as a lyophilizate.

In the manner as described in Example 1 using the corresponding reactants the following compounds are obtained, chromatographic purification may be carried out optionally.

TABLE 1:

W is N except for ex. 4, 5 and 24 wherein W = CH,

R_1 is O-CH_2-F except for ex.4 wherein R_1 is OH, ex. 5 wherein R_1 is O-CH_3 and for ex. 24 wherein R_1 is O-$CH(CH_3)_2COOH$,

R_2 is H,

R_3 is H for ex. 7-11, 14-18, CH_3 for ex. 2-5, 12-13, 19-28, CH_2-CH_3 for ex. 3, CH_2-CH=CH_2 for ex. 6, cyclopropyl for ex.29 and

R_4 is H except for ex.14 wherein R_4 is CH_3

All compounds are in trans conformation, except example 2 (= cis).

Example	X	R_5	R_6	R_7	N-$R_5R_6R_7$ position
2	NH	H	H	-	p
3	NH	H	H	-	p
4	NH	H	H	-	p
5	NH	H	H	-	p

6	NH	H	H	-	p
7	NH	H	H	-	o
8	NH	H	H	-	p
9	NH	CH_3	CH_3	-	p
10	NH	CH_3	CH_3	CH_3	p
11	N-CH_3	H	H	-	o
12	NH	CH_3	CH_3	CH_3	p
13	NH	-SO_2-Phe-NH_2(p)	-	-	p
14	N-CH_3	CH_3	-	-	p
15	N-CH_3	H	H	-	p
16	N-CH_3	CH_3	CH_3	-	p
17	N-CH_3	CH_3	CH_3	CH_3	p
18	N-CH_3	H	H	-	o
19	N-cyclohexyl-NH_2(p)	H	H	-	p
20	NH	H	H	-	m
21	NH	H	H	-	m
22	NH	H	H	-	m
23	NH	H	H	-	m
24	NH	H	H	-	p
25	S	H	H	-	p
26	O	H	H	-	p
27	NH	H	H	-	m
28	N-CH_3	H	H	-	p
29	NH	H	H	-	p

Example 30:

3-{(E)[[1-trans-(4-acetylamino-cyclohexylamino)-iminomethyl]-methylhydrazono] methyl}-7-{[(5-amino-1,2,4-thiadiazol-3-yl)-(Z)-(fluoromethoxyimino)-acetyl]amino}-3-cephem-4-carboxylic acid dihydrochloride

A suspension of 0.2579 g of 3-{(E)[[1-trans-(4-amino-cyclohexylamino)-iminomethyl]-methylhydrazono]methyl}-7-{[(5-amino-1,2,4-thiadiazol-3-yl)-(Z)-(fluoromethoxyimino)-acetyl]amino}-3-cephem-4-carboxylic acid trihydrochloride in 20 ml acetonitrile is dissolved with 0.6395 g of N,O-bis-(trimethylsilyl)-acetamid. After adding 0.026 ml acetylchloride and

stirring, 0.115 ml of water are added. A precipitate formed is filtered, washed and dried and 3-{(E)[[1-trans-(4-acetylamino-cyclohexylamino)-iminomethyl]-methylhydrazono]methyl}-7-{2-(5-amino-[1,2,4]thiadiazol-3-yl)-2-[(Z)-fluoromethoxyimino]-acetylamino}-cephem-4-carboxylic acid in the form of a dihydrochloride is obtained.

In the manner as described in example 30 and using the corresponding reactants the following compounds are obtained:

TABLE 2:

W is N, R_1 is O-CH_2-F, R_2 is H, R_3 is CH_3 and R_4 is H

Example	X	R_5	R_6	R_7	N-$R_5R_6R_7$ position
31	NH	-CO-phe	-	-	p
32	NH	-CO-phe-$OCOCH_3$(o)	-	-	p
33	NH	-CO-CH_2-O-phe	-	-	p
34	NH	-SO_2-phe-$NHCOCH_3$(p)			p
35	NH	-CO-CH_2-thiophene(2)	-	-	p

Example 36

3-{(E)[[(trans-4-aminocyclohexylimino)methylthiomethyl]methylhydrazono]methyl}-7-{[(5-amino-1,2,4-thiadiazol-3-yl)-(Z)-(fluoromethoxyimino)-acetyl]amino}-3-cephem-4-carboxylic acid

a) 3-{(E)[[trans-4-((1,1-dimethylethoxy)carbonyl)aminocyclohexylimino) methylthiomethyl]methylhydrazono]methyl}-7-{[(5-amino-1,2,4-thiadiazol-3-yl)-(Z)-(fluoromethoxyimino)-acetyl]amino}-3-cephem-4-carboxylic acid

To a solution of 0.144 g of N-(1,4,5a,6-tetrahydro-3-hydroxy-1,7-dioxo-3 H,7 H-azeto(2,1-b)furo(3,4-d)(1,3)-thiazin-6-yl)-2-(5-amino-1,2,4-thiadiazol-3-yl)-(Z)-2-(fluoromethoxyimino) acetic acid amide in 0.5 ml dimethylacetamide a solution of 0.103 g of [trans-4-(3-amino-2,3-dimethyl-isothioureido)cyclohexyl]-carbamic acid tert-butyl ester in 2.5 ml dimethylacetamide is added. After stirring at RT 0.165 ml 2 N HCl are added and a mixture formed is stirred at RT. The mixture obtained is poured onto tert-butyl-methyl-ether and stirred at RT.
A precipitate obtained is filtered, washed and dried. 3-{(E)[[trans-4-((1,1-dimethylethoxy) carbonyl)aminocyclohexylimino)methylthiomethyl]methylhydrazono]methyl}-7-{[(5-amino-

1,2,4-thiadiazol-3-yl)-(Z)-(fluoromethoxyimino)-acetyl]amino}-3-cephem-4-carboxylic acid in the form of a hydrochloride is obtained.

b) 3-{(E)[[(trans-4-aminocyclohexylimino)methylthiomethyl]methylhydrazono] methyl}-7-{[(5-amino-1,2,4-thiadiazol-3-yl)-(Z)-(fluoromethoxyimino)-acetyl]amino}-3-cephem-4-carboxylic acid

After cooling a suspension of 0.235 g 3-{(E)[[trans-4-((1,1-dimethylethoxy)carbonyl)amino-cyclohexylimino)methylthiomethyl]methylhydrazono]methyl}-7-{[(5-amino-1,2,4-thiadiazol-3-yl)-(Z)-(fluoromethoxyimino)-acetyl]amino}-3-cephem-4-carboxylic acid hydrochloride in 2 ml dichloromethane to 0°C 2 ml of trifluoracetic acid are added.
After stirring a solution obtained, solvent is evaporated, a residue formed is treated with water and a precipitate formed is filtered. After lyophilizing a filtrate the residue obtained is treated with water and 2 N HCl. The solution formed is subjected to a chromatography column (e.g. Li Chroprep RP-18^R, Merck) and eluated. Fractions containing the desired compound (determined by HPLC) are combined and lyophilised.
3-{(E)[[(Trans-4-aminocyclohexylimino)methylthiomethyl]methylhydrazono]methyl}-7-{[(5-amino-1,2,4-thiadiazol-3-yl)-(Z)-(fluoromethoxyimino)-acetyl]amino}-3-cephem-4-carboxylic acid in the form of a hydrochloride is obtained.

Example 37:

SYNTHESIS OF INTERMEDIATE COMPOUNDS

Procedure A

3-amino-1-(trans-4-aminocyclohexyl)-guanidine dihydrochloride

a) [trans-4-(3-ethoxycarbonyl-thioureido)cyclohexyl]carbamic acid tert-butyl ester

To a solution of 1.10 g (4-amino-cyclohexyl)-carbamic acid tert-butyl ester in 25 ml acetic acid ethyl ester 0.58 ml ethoxycarbonyl-isothiocyanat are added and stirred at RT.
The precipitate formed is filtered and washed with diethylether to give 1.31 g of [trans-4-(3-Ethoxycarbonyl-thioureido)cyclohexyl]carbamic acid tert-butyl ester.

b) (trans-4-thioureido-cyclohexyl)-carbamic acid tert-butyl ester

To a suspension of 1.69 g [trans-4-(3-ethoxycarbonyl-thioureido)cyclohexyl]carbamic acid tert-butyl ester in 10 ml water and 15 ml ethanol 7.4 ml 4 M NaOH are added. The resulting mixture is kept at 90°C for 30 minutes. The precipitate formed at RT is filtered and washed with diethylether. 1.19 g of (trans-4-thioureido-cyclohexyl)-carbamic acid tert-butyl ester are obtained as a solid.

c) [trans-4-(2-methyl-isothioureido)-cyclohexyl]-carbamic acid tert-butyl ester hydroiodide

A mixture of 1.19 g of (trans-4-thioureido-cyclohexyl)-carbamic acid tert-butyl ester and 0.41 ml methyliodide in 50 ml methanol is stirred at RT. Solvent is evaporated to give 2.06 g of [trans-4-(2-methyl-isothioureido)-cyclohexyl]-carbamic acid tert-butyl ester hydroiodide.

d) [trans-4-(2-methyl-isothioureido)-cyclohexyl]-carbamic acid tert-butyl ester hydrochloride

To a suspension of 2.06 g of [trans-4-(2-methyl-isothioureido)-cyclohexyl]-carbamic acid tert-butyl ester in the form of a hydroiodide in 50 ml water 40 ml of a strong basic ion exchanger in chloride form (Amberlite IRA 400 $(Cl)^R$) are added. After stirring the mixture at RT the ion exchanger is filtered and the filtrate is lyophilised to give [trans-4-(2-methyl-isothioureido)-cyclohexyl]-carbamic acid tert-butyl ester in the form of a hydrochloride

e) [trans-4-((hydrazino)iminomethyl)aminocyclohexyl]-carbamic acid tert-butyl ester hydrochloride

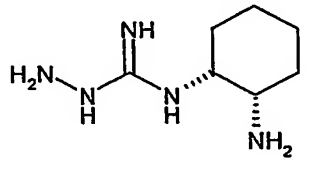
To a solution of 1.11 g [trans-4-(2-methyl-isothioureido)-cyclohexyl]-carbamic acid tert-butyl ester in 50 ml ethanol 0.183 ml hydrazine monohydrate are added. After refluxing the reaction mixture solvent is evaporated and [trans-4-(hydrazino)iminomethyl) aminocyclohexyl]-carbamic acid tert-butyl ester in the form of a hydrochloride is obtained.

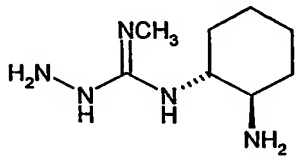
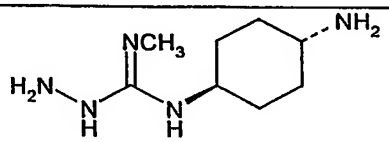
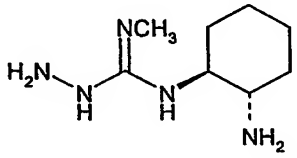
f) 3-amino-1-(trans-4-aminocyclohexyl)-guanidine dihydrochloride

A reaction mixture of 1.15 g [trans-4-(hydrazino)iminomethyl)-aminocyclohexyl]-carbamic acid tert-butyl ester in the form of a hydrochloride and 4.2 ml 5.4 M HCl (in methanol) in 50 ml methanol is stirred at RT. The volume of the mixture is reduced and a precipitate formed is filtered to give 3-amino-1-(trans-4-aminocyclohexyl)-guanidine in the form of a dihydrochloride.

In the manner as described in procedure A, but using the corresponding reactants the following compounds are obtained:

TABLE 3:

Example	compound formula
A2	

A3	
A4	
A5	

Procedure B

3-amino-2-(trans-4-dimethylaminocyclohexyl)-1-methyl-guanidine dihydrochloride

a) 1-(trans-4-dimethylaminocyclohexyl)-3-methyl-thiourea

To a solution of 1.74 g trans-4-dimethylaminocyclohexanamine in 50 ml acetic acid ethyl ester 0.90 g methyl-isothiocyanate are added. After stirring the mixture obtained at RT solvent is evaporated and 1-(4-dimethylaminocyclohexyl)-3-methyl-thiourea is obtained.

b) 1-(trans-4-dimethylaminocyclohexyl)-2,3-dimethyl-isothiourea hydrochloride

A mixture of 0.50 g 1-(4-dimethylaminocyclohexyl)-3-methyl-thiourea in 10 ml methanol, after adding 1.16 ml 2 M HCl (in methanol) and 0.36 g methyliodide is stirred at RT.

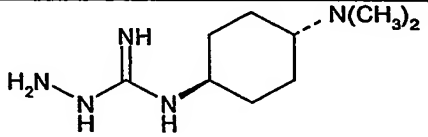
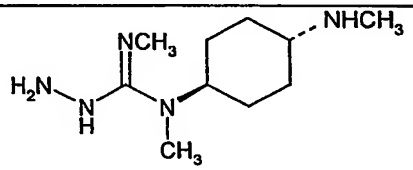
Solvent is evaporated and a residue formed is taken up in water. 10 ml of a strong basic ion exchanger in chloride form (Amberlite IRA 400 $(Cl)^R$) are added. After stirring the mixture at RT a filtrate is lyophilised to give 1-(4-dimethylamino cyclohexyl)-2,3-dimethyl-isothiourea in the form of a hydrochloride.

c) 3-amino-2-(trans-4-dimethylaminocyclohexyl)-1-methyl-guanidine dihydrochloride

A solution of 0.71 g 1-(4-dimethylaminocyclohexyl)-2,3-dimethyl-isothiourea hydrochloride in 40 ml ethanol absolute and 0.126 ml hydrazine monohydrate is refluxed. Solvent is then evaporated and 3-amino-2-(trans-4-dimethylaminocyclohexyl)-1-methyl-guanidine in the form of a dihydrochloride is obtained in the form of a white solid.

In the manner as described in procedure B, but using the corresponding reactants the following compounds may be obtained

TABLE 4:

Example	compound formula
B2	
B3	

Procedure C

[trans-4-((hydrazino)methyliminomethyl)aminocyclohexyl]-trimethyl-ammonium chloride hydrochloride

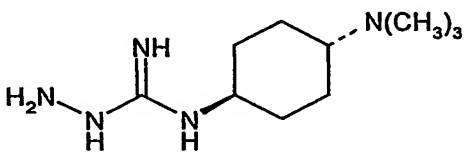
a) [trans-4-(2,3-dimethyl-isothioureido)-cyclohexyl]-trimethyl-ammonium hydrochloride

A mixture of 0.50 g 1-(4-dimethylamino-cyclohexyl)-3-methyl-thiourea in 20 ml methanol and 0.36 ml methyliodide is stirred at RT. After refluxing a mixture obtained, solvent is evaporated. A residue formed is taken up in water, stirred over a strong basic ion exchanger in chloride form (Amberlite IRA 400 $(Cl)^R$), filtered and lyophilised to give [trans-4-(2,3-dimethyl-isothioureido)-cyclohexyl]-trimethyl-ammonium in the form of a hydrochloride.

b) [trans-4-((hydrazino)methyliminomethyl)aminocyclohexyl]-trimethyl-ammonium chloride hydrochloride

A solution of [trans-4-(2,3-dimethyl-isothioureido)-cyclohexyl]-trimethyl-ammonium hydrochloride in ethanol after adding 0.118 ml hydrazin monohydrate is refluxed and solvent is evaporated. [Trans-4-((hydrazino)methyliminomethyl)aminocyclo hexyl]-trimethyl-ammonium chloride in the form of a hydrochloride is obtained.

In the manner as described in procedure C, but using the corresponding reactants the following compound is obtained:



Procedure D

3-amino-bis-1,2-(trans-4-aminocyclohexyl)-3-methyl-guanidine trihydrochloride

a) Benzylidene derivative of 3-amino-bis-1,2-(trans-4-aminocyclohexyl)-3-methyl-guanidine dihydrochloride

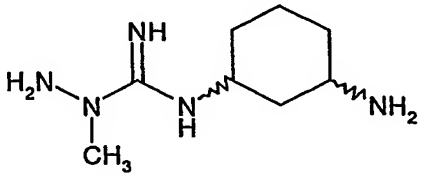
Reacting the benzylidene derivative of S-methyl-2-methyl-isothiosemicarbazide with trans-1,4-diaminocyclohexane in the manner already described for the preparation of the benzylidene derivative of 3-amino-1-(trans-4-aminocyclohexyl)-3-methyl-guanidine in the form of a monohydrochloride yields 1.5% benzylidene derivative of 3-amino-bis 1,2-(trans-4-aminocyclohexyl)-3-methyl-guanidine trihydrochloride (determined by HPLC at 254 nm) as a site product. This site.product is purified by e.g. column chromatography (Li Chroprep RP-18^R, Merck). Enriched samples of benzylidene derivative of 3-amino-bis-1,2-(trans-4-aminocyclohexyl)-3-methyl-guanidine dihydrochloride are dissolved in water, poured on the column and eluated. Fractions containing the desired product (determined by HPLC) are combined and solvent is evaporated. Benzylidene derivative of 3-amino-bis-1,2-(trans-4-aminocyclohexyl)-3-methyl-guanidine in the form of a dihydrochloride is obtained.

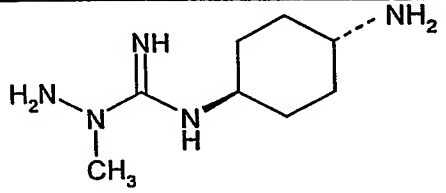
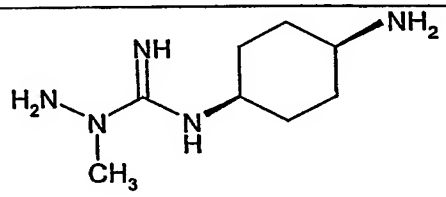
b) 3-amino-bis-1,2-(trans-4-aminocyclohexyl)-3-methyl-guanidine-trihydrochloride

Removing the benzylidene protecting group proceeds in the same manner already described for 3-amino-1-(trans-4-aminocyclohexyl)-3-methyl-guanidine in the form of a dihydrochloride.

In the manner as described in procedure D, but using the corresponding reactants the following compounds may be obtained:

TABLE 5:

Example	compound formula
D2-D5 und D8	

D6	
D7	

Procedure E

[trans-4-((1-methylhydrazino)iminomethyl)aminocyclohexyl]-trimethyl-ammonium chloride hydrochloride

a) Benzylidene derivative of 3-amino-1-(trans-4-aminocyclohexyl)-3-methyl-guanidine

The pH of a solution of 5 g of the benzylidene derivative of 3-amino-1-(trans-4-aminocyclo hexyl)-3-methyl-guanidine in the form of a monohydrochloride in of water is adjusted to pH 13.6 by addition of 8 N NaOH. The mixture obtained is extracted with dichloromethane. The organic phase is dried and solvent is evaporated to give a benzylidene derivative of 3-amino-1-(trans-4-aminocyclohexyl)-3-methyl-guanidine.

b) Benzylidene derivative of [trans-4-((1-methylhydrazino)iminomethyl))aminocyclohexyl]-trimethyl-ammonium chloride

To a solution of 1 g of the benzylidene derivative of 3-amino-1-(trans-4-aminocyclohexyl)-3-methyl-guanidine in acetonitrile 1.295 g methyliodide in 10 ml acetonitrile are added.The mixture obtained is refluxed and stirred at RT. Solvent is evaporated, the residue is taken up in water and treated with 20 ml of a strong basic ion exchanger in chloride form (Amberlite IRA 400 $(Cl)^R$). A suspension formed is stirred at RT, filtered and a filtrate formed is lyophilised.The lyophilizate is resolved in water and the pH of the solution is adjusted to 13.4 with 8 N NaOH. After extracting with dichloromethane, the water phase is adjusted to pH 2 with 8 N HCl and lyophilised. The lyophilisate is dissolved in water, subjected to e.g. a chromatography column, which filled with RP-18^R (Li Chroprep RP-18^R, grain size 40-63 µm, Merck), and eluated with water. Fractions (examined by means of analytical HPLC) containing the desired product are collected and lyophilised to obtain benzylidene derivative of [trans-4-((1-methyl hydrazino)(imino-methyl))aminocyclohexyl]-trimethyl-ammonium chloride.

c) [trans-4-((1-methylhydrazino)iminomethyl)aminocyclohexyl]-trimethyl-ammonium chloride hydrochloride

A mixture of benzylidene derivative of [trans-4-((1-methylhydrazino)(iminomethyl))aminocyclo hexyl]-trimethyl-ammonium chloride in 1.7 ml 2 N HCl and water is treated by steam destillation. After evaporation of solvent [trans-4-((1-methylhydrazino)iminomethyl) aminocyclohexyl]-trimethyl-**ammonium chloride hydrochloride ????** is obtained.

Procedure F

3-amino-1-(trans-4-aminocyclohexyl)-3-ethyl-guanidine dihydrochloride

a) Benzylidene derivative of [trans-4-((hydrazino)iminomethyl)aminocyclohexyl]-1-N-formamid

A mixture of 5.5 ml acetic anhydride and 11.2 ml formic acid is stirred at 0°C. A solution of 5.04 g benzylidene derivative of 3-amino-1-(trans-4-aminocyclohexyl)-guanidine (preparation of the free base is done in the same manner described in procedure E a) in 5.6 ml formic acid is added to the mixed anhydride. After stirring a mixture formed solvent is evaporated. A residue is treated with water and the pH of a solution formed is adjusted to 13.02 with 2 N NaOH. A precipitate formed is filtered off, washed with water and dried to give benzylidene derivative of [trans-4-((hydrazino)iminomethyl)amino cyclohexyl]-1-N-formamid.

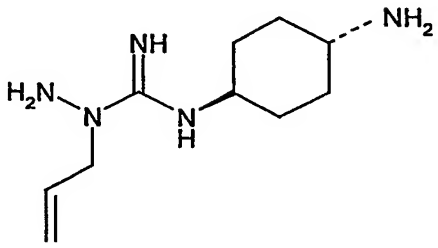
b) Benzylidene derivative of [trans-4-((1-ethylhydrazino)iminomethyl)aminocyclohexyl]-1-N-formamid hydroiodide

After adding 0.28 ml ethyliodide to a solution of 0.5 g of the benzylidene derivative of [trans-4-((1-hydrazino)(iminomethyl)aminocyclohexyl]-N-formamid the mixture is refluxed. Keeping the mixture over night at RT and adding ethyliodide following by refluxing the mixture and again keep the resulting mixture at RT results in a precipitate, which is filtered and dried. Benzylidene derivative of [trans-4-((1-ethylhydrazino)iminomethyl)amino cyclohexyl]-1-N-formamid in the form of a hydroiodide is obtained.

c) 3-amino-1-(trans-4-aminocyclohexyl)-3-ethyl-guanidine dihydrochloride

A suspension of 0.34 g of benzylidene derivative of [trans-4-((1-ethylhydrazino)iminomethyl) aminocyclohexyl]-1-N-formamid hydroiodide in 10 ml water and 10 ml strong basic ion exchanger in chloride form (Amberlite IRA 400 $(Cl)^R$) is stirred. After filtration and adding 2 ml 2 N HCl to the filtrate benzaldehyde is destilled. Solvent is evaporated and 3-amino-1-(trans-4-aminocyclohexyl)-3-ethyl-guanidine in the form of a dihydrochloride is obtained.

In the manner as described in procedure F, but using the corresponding reactants the following compound is obtained:



Procedure G

4-amino-N-[trans-4-((1-methylhydrazino)iminomethyl)aminocyclohexyl]-benzene-sulfonamide dihydrochloride

a) Benzylidene derivative of N-[4-[-trans-4-((1-methylhydrazino)iminomethyl)] aminocyclo hexylsulfamoyl)-phenyl]-acetamid

To a suspension of 0.5 g benzylidene derivative of 3-amino-1-(trans-4-aminocyclohexyl)-3-methyl-guanidine in acetonitrile 2.37 ml N,O-bis-(trimethylsilyl)-acetamide are added. A solution obtained is treated with 0.378 g of 4-acetylamino-benzenesulfonyl chloride and stirred at RT. After adding of 3.49 ml water/acetonitrile a precipitate formed is filtered and washed with acetonitrile. Benzylidene derivative of N-[4-[-trans-4-((1-methylhydrazino) iminomethyl)]aminocyclohexylsulfamoyl)-phenyl]-acetamid is obtained.

b) 4-amino-N-[trans-4-((1-methylhydrazino)iminomethyl)aminocyclohexyl]-benzene-sulfonamide dihydrochloride

From a suspension of 0.62 g benzylidene derivative of N-[4-[trans-4-((1-methylhydrazino) iminomethyl)]aminocyclohexylsulfamoyl)-phenyl]-acetamid 3.4 ml 1 N HCl and water, benzaldehyde and acetic acid is split off. An aqueous solution obtained is concentrated and dried. 4-Amino-N-[trans-4-((1-methylhydrazino)iminomethyl)aminocyclohexyl]-benzene-sulfonamide in the form of a dihydrochloride is obtained.

Procedure H

3-amino-1-(trans-4-aminocyclohexyl)-2,3-dimethyl-guanidine dihydrochloride

a) [trans-4-(3-amino-3-methyl-thioureido)cyclohexyl]-carbamic acid tert-butyl ester

To a solution of 2 g (trans-4-isothiocyanate-cyclohexyl)-carbamic acid tert-butyl ester 0.49 ml methylhydrazine are added. After stirring at RT petrolether is added. A precipitate formed is

filtered, washed and dried. [Trans-4-(3-amino-3-methyl-thioureido) cyclohexyl]-carbamic acid tert-butyl ester is obtained.

b) [trans-4-(3-amino-2,3-dimethyl-isothioureido)cyclohexyl]-carbamic acid tert-butyl ester hydrochloride

A suspension of 1.17 g of [trans-4-(3-amino-3-methyl-thioureido)cyclohexyl]-carbamic acid tert-butyl ester in 30 ml methanol is treated with 0.34 ml methyliodide. After refluxing solvent is evaporated. The residue is suspended in water and treated with a strong basic ion exchanger in chloride form (Amberlite IRA 400 $(Cl)^R$). After stirring at RT the ion exchanger is filtered off and the filtrate is lyophilised. [Trans-4-(3-amino-2,3-dimethyl-isothioureido) cyclohexyl]-carbamic acid tert-butyl ester in the form of a hydrochloride is obtained.

c) Benzylidene derivative of [trans-4-(3-amino-2,3-dimethyl-isothioureido)cyclohexyl]-carbamic acid tert-butyl ester hydrochloride

To a solution of 0.40 g [trans-4-(3-amino-2,3-dimethyl-isothioureido)cyclohexyl]-carbamic acid tert-butyl ester hydrochloride in 20 ml water and 30 ml acetonitrile 1.3 ml 2 N HCl and 0.15 ml benzaldehyde is added. After stirring the mixture acetonitrile is evaporated and solution obtained is extracted with ether. After adjusting the pH of the aqueous phase to 7 a precipitate formed is filtered, washed and dried. Benzylidene derivative of [trans-4-(3-amino-2,3-dimethyl-isothioureido)cyclohexyl]-carbamic acid tert-butyl ester in the form of a hydrochloride is obtained.

d) Benzylidene derivative of [trans-4-(1-methylhydrazino)(methyliminomethyl) aminocyclo hexyl]-carbamic acid tert-butyl ester

A suspension of 0.2 g of benzylidene derivative of [trans-4-(3-amino, 2,3-dimethyl-isothioureido)-cyclohexyl]-carbamic acid tert-butylester hydrochloride is treated with 0.126 ml methylamine and stirred. Solvent is evaporated from the clear solution and benzylidene derivative of [trans-4-(1-methylhydrazino)(methyl iminomethyl)aminocyclohexyl]-carbamic acid tert-butylester is obtained.

e) Benzylidene derivative of 3-amino-1-(trans-4-aminocyclohexyl)-2,3-dimethyl-guanidine trifluoroacetate

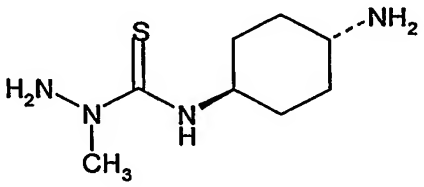
To a solution of 0.2 g benzylidene derivative of [trans-4-(1-methylhydrazino)(methylimino methyl)aminocyclohexyl]-carbamic acid tert-butyl ester in 10 ml dichloromethane at 0°C 10 ml of trifluoroacetic acid are added. After stirring at RTsolvent is evaporated and a benzylidene derivative of 3-amino-1-(trans-4-aminocyclohexyl)-2,3-dimethyl-guanidine trifluoroacetate is obtained.

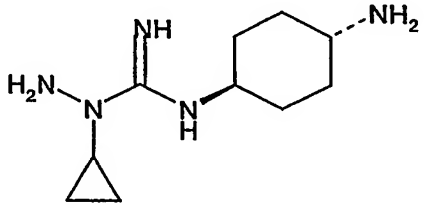
f) 3-amino-1-(trans-4-aminocyclohexyl)-2,3-dimethyl-guanidine dihydrochloride

From a solution of 0.2 g of benzylidene derivative of 3-amino-1-(trans-4-aminocyclohexyl)-2,3-dimethyl-guanidine trifluoroacetate in water and after addition of 1.6 ml 1 N HCl benzaldehyde is splitted off. After reducing the volume of the resulting mixture 20 ml strong basic ion exchanger in chloride form (Amberlite IRA 400 $(Cl)^R$) is added.

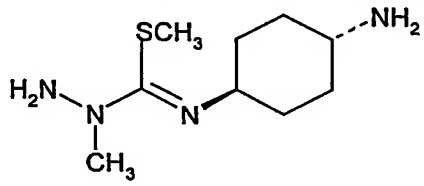
After stirring, filtration and evaporating solvent 3-amino-1-(trans-4-aminocyclo hexyl)-2,3-dimethyl-guanidine in the form of a dihydrochloride is obtained.

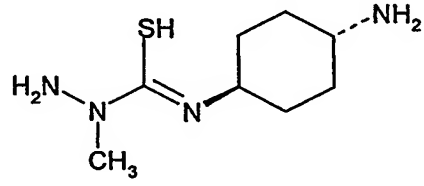
In the manner as described in procedure H, but using the corresponding reactants the following compounds are obtained:





(tert-Butyloxycarbonyl protecting group in procedure H a) is removed with HCl in methanol)





(tert-Butyloxycarbonyl protecting group is removed with trifluoroacetic acid)

Procedure I

[3-amino-1-(trans-4-aminocyclohexyl)-3-methyl]-urea dihydrochloride

a) [trans-4-(3-amino-3-methyl-ureido)cyclohexyl-carbamic acid tert-butyl ester

A solution of 0.435 g [trans-4-(3-amino-2,3-dimethyl-isothioureido)cyclohexyl]-carbamic acid tert-butyl ester hydrochloride is treated with 0.18 ml ammonia (2 M in ethanol) and the mixture obtained is refluxed. After stirring at RT solvent is evaporated and [trans-4-(3-amino-3-methyl-ureido)cyclohexyl-carbamic acid tert-butyl ester is obtained.

b) [3-amino-1-(trans-4-aminocyclohexyl)-3-methyl]-urea dihydrochloride

A mixture of 0.34 g of [trans-4-(3-amino-3-methyl-ureido)cyclohexyl-carbamic acid tert-butyl ester in 15 ml methanol and 2 ml 2 N HCl (in methanol) is stirred at RT for 4 hours. After evaporating solvent a residue formed is taken up in water, the pH is adjusted to 2 with 2 N HCl and a precipitate formed is filtered. After lyophilising a filtrate obtained [3-amino-1-(trans-4-aminocyclohexyl)-3-methyl]-urea in the form of a dihydrochloride is obtained.

^{1}H-NMR-Spectra

(200 MHz, in DMSO-d_6 unless given otherwise)

1 1.30 – 1.70, m, 4H, CCH_2; 1.80 – 2.10, m, 4H, CCH_2; 2.88 –3.10, m, 1H, NCH; 3.32, s, 3H, NCH_3; 3.42 – 3.70, m, 2H, 1H from SCH_2 and 1H from NCH; 4.25, part of the AB-quartet, J=18 Hz, 1H, SCH_2; 5.28, d, J=5 Hz, 1H, ß-lactam; 5.79, d, J=55 Hz, 2H, CH_2F; 5,75, dd, J=5 Hz and 8 Hz, 1H, ß-lactam; 8.10, s, 1H, CH=N; 9.84, d, J=8 Hz, 1H, NH

2 1.40 – 2.12, m, 8H, CCH_2; 3.10 – 3.30, m, 1H, NCH; 3.35, s, 3H, NCH_3; 3.55 and 4.54, AB-quartet, J=18 Hz, 2H, SCH_2; 3.75 – 3.95, m, 1H, NCH; 5.15, d, J=5 Hz, 1H, ß-lactam; 5.77, d, J=55 Hz, 2H, CH_2F; 5.78, dd, J=5 Hz and 8 Hz, 1H, ß-lactam; 8.12, s, 1H, CH=N; 9.86, d, J=8 Hz, 1H, NH

3 1.06, t, J=5 Hz, 3H, CH_3; 1.32 – 1.70, m, 4H, CCH_2; 1.75 – 2.12, m, 4H, CCH_2; 2.88 – 3.10, m, 1H, NCH; 3.48 – 3.72, m, 2H, 1H from SCH_2 and 1H from NCH; 3.98, m, 2H, NCH_2; 4.24, part of the AB-quartet, J=18 Hz, 1H, SCH_2; 5.14, d, J=5 Hz, 1H, ß-lactam; 5.79, d, J=55 Hz, 2H, CH_2F; 5.77, dd, J=5 Hz and 8 Hz, 1H, ß-lactam; 8.12, s, 1H, CH=N; 9.84, d, J=8 Hz, 1H, NH

4 (in D_2O) 1.28 – 1.65, m, 4H, CCH_2; 1.80 – 2.10, m, 4H, CCH_2; 2.82 – 3.08, m, 1H, NCH; 3.32 – 3.60, m, 2H, 1H from NCH_2 and 1H from SCH_2; 4.14, part of the AB-quartet, J=18 Hz, 1H, SCH_2; 5.09, d, J=5 Hz, 1H, ß-lactam; 5.69, d, 1H, ß-lactam; 6.65, s, 1H, CH thiazol; 8.21, s, 1H, CH=N

5 1.35 – 1.68, m, 4H, CCH_2; 1.78 – 2.12, m, 4H, CCH_2; 2.82 – 3.06, m, 1H, NCH; 3.35, s, 3H, NCH_3; 3.50 – 3.80, m, 2H, 1H from NCH and 1H from SCH_2; 3.90, s, 3H, OCH_3; 4.58, part of the AB-quartet, J=18 Hz, 1H, SCH_2; 5.28, d, J=5 Hz, 1H, ß-lactam; 5.90, dd, J=5 Hz and 8 Hz, 1H, ß-lactam; 6.85, s, 1H, CH thiazol; 8.08, s, 1H, CH=N; 9.79, d, J=8 Hz, 1H, NH

6 1.30 – 1.70, m, 4H, CCH_2; 1.82 – 2.08, m, 4H, CCH_2; 2.88 – 3.10, m, 1H, NCH; 3.40 – 3.68, m, 2H, 1H from NCH and 1H from SCH_2; 4.42 – 4.78, m, 3H, 2H from NCH_2 and 1H from SCH_2; 4.92 – 5.35, m, 3H, 1H from ß-lactam and 2H from CH_2=C; 5.52 – 6.04, m, 4H, 1H from ß-lactam, 1H from C–CH=C and 2H from CH_2F; 8.08, s, 1H, CH=N; 9.84, d, J=8 Hz, 1H, NH

7 1.15 – 1.50, m, 4H, CCH_2; 1.60 – 1.82, m, 2H, CCH_2; 1.88 – 2.20, m, 2H, CCH_2; 3.00 – 3.30, m, 1H, NCH; 3.45 – 3.75, m, 2H, 1H from NCH and 1H from SCH_2; 4.52, part of the AB-quartet, J=18 Hz, 1H, SCH_2; 5.28, d, J=5 Hz, 1H, ß-lactam; 5.78, d, J=55 Hz, 2H, CH_2F; 5.92, dd, J=5 Hz and 8 Hz, 1H, ß-lactam; 8.32, s, 1H, CH=N; 9.82, d, J=8 Hz, 1H, NH

8 1.28 – 1.62, m, 4H, NCH_2; 1.78 – 2.12, m, 4H, NCH_2; 2.88 – 3.12, m, 1H, NCH; 3.40 – 3.70, m, 2H, 1H from NCH and 1H from SCH_2; 4.48, part of the AB-quartet, J=18 Hz, 1H, SCH_2; 5.27, d, J=5 Hz, 1H, ß-lactam; 5.77, d, J=55 Hz, 2H, CH_2F; 5.90, dd, J=5 Hz and 8 Hz, 1H, ß-lactam; 8.28, s, 1H, CH=N; 10.82, d, J=8 Hz, 1H, NH

9 1.20 – 1.65, m, 4H, CCH_2; 1.90 – 2.12, m, 4H, CCH_2; 2.75, b, 6H, NCH_3; 3.00 – 3.60, m, 3H, 2 from NCH and 1H from SCH_2; 4.32, part of the AB-quartet, J=18 Hz, 1H, SCH_2; 5.22, d, J=5 Hz, 1H, ß-lactam; 5.79, d, J=55 Hz, 2H, CH_2F; 5.80, dd, J=5 Hz and 8 Hz, 1H, ß-lactam; 8.22, s, 1H, CH=N; 9.78, d, J=8 Hz, 1H, NH

10 1.30 – 1.70, m, 4H, CCH_2; 1.92 – 2.32, m, 4H, CCH_2; 3.05, b, 9H, NCH_3; 3.20 – 3.68, m, 3H, 2H from NCH and 1H from SCH_2; 4.48, part of the AB-quartet, J=18 Hz, 1H, SCH_2; 5.28, d, J=5 Hz, 1H, ß-lactam; 5.78, d, J=55 Hz, 2H, CH_2F; 5.94, dd, J=5 Hz and 8 Hz, 1H, ß-lactam; 8.30, s, 1H, CH=N; 9.84, d, J=8 Hz, 1H, NH

11 1.15 – 1.58, m, 4H, CCH_2; 1.65 – 2.30, m, 4H, CCH_2; 2.92, s, 3H, NCH_3; 3.08 – 3.75, m, 3H, 2H from NCH and 1H from SCH_2; 4.48, part of the AB-quartet, J=18 Hz, 1H, SCH_2; 5.32, d, J=5 Hz, 1H, ß-lactam; 5.77, d, J=55 Hz, 2H, CH_2F; 5.95, dd, J=5 Hz and 8 Hz, 1H, ß-lactam; 8.52, s, 1H, CH=N; 9.82, d, J=8 Hz, 1H, NH

12 1.40 – 1.75, m, 4H, CCH_2; 1.92 – 2.32, m, 4H, CCH_2; 3.04, b, 9H, NCH_3; 3.25 – 3.80, m, 6H, 3H from NCH_3 and 2H from NCH and 1H from SCH_2; 4.58, part of the AB-quartet, J=18 Hz, 1H, SCH_2; 5.27, d, J=5 Hz, 1H, ß-lactam; 5.78, d, J=55 Hz, 2H, CH_2F; 5.96, dd, J=5 Hz and 8 Hz, 1H, ß-lactam; 8.07, s, 1H, CH=N; 9.86, d, J=8 Hz, 1H, NH

13 1.10 – 1.45, m, 4H, CCH_2; 1.55 – 1.88, m, 4H, CCH_2; 2.65 – 2.95, m, 1H, NCH; 3.28, s, 3H, NCH_3; 3.32 – 3.60, m, 2H, 1H from NH and 1H from SCH_2; 4.50, part of the AB-quartet, J=18 Hz, 1H, SCH_2; 5.26, d, J=5 Hz, 1H, ß-lactam; 5.77, d, J=55 Hz, 2H, CH_2F; 5.96, dd, J=5 Hz and 8 Hz, 1H, ß-lactam; 6.60, d, J=9 Hz, 2H, aromatic-H; 7.42, d, J=9 Hz, 2H, aromatic-H; 8.07, s, 1H, CH=N; 9.75, d, J=8 Hz, 1H, NH

14 1.30 – 1.58, m, 2H, CCH_2; 1.62 – 1.88, m, 4H, CCH_2; 2.00 – 2.22, m, 2H, CCH_2; 2.54, s, 3H, NCH_3; 2.72 – 3.10, m, 7H, 6H from NCH_3 and 1H from NCH; 3.48-3.72, m, 2H, 1H from NCH and 1H from SCH_2; 4.10, part of the AB-quartet, J=18 Hz, 1H, SCH_2; 5.28, d, J=5 Hz, 1H, ß-lactam; 5.77, d, J=55 Hz, 2H, CH_2F; 5.94, dd, J=5 Hz and 8 Hz, 1H, ß-lactam; 8.47, s, 1H, CH=N; 9.84, d, J=8 Hz, 1H, NH

15 1.30 – 1.70, m, 4H, CCH_2; 1.72 – 2.10, m, 4H, CCH_2; 2.70 – 3.10, m, 4H, 3H from NCH_3 and 1H from NCH; 3.35 – 3.70, m, 2H, 1H from NCH and 1H from SCH_2; 3.50, part of the AB-quartet, J=18 Hz, 1H, SCH_2; 5.28, d, J=5 Hz, 1H, ß-lactam; 5.78, dd, J=55 Hz, 2H, CH_2F; 5.94, dd, J=5 Hz and 8 Hz, 1H, ß-lactam; 8.55, s, 1H, CH=N; 9.85, d, J=8 Hz, 1H, NH

16 1.32 – 1.70, m, 4H, CCH_2; 1.80 – 2.20, m, 4H, CCH_2; 2.70, b, 6H, NCH_3; 2.88, d, 3H, NCH_3; 3.00 – 3.20, m, 1H, NCH; 3.38 – 3.70, m, 2H, 1H from NCH and 1H from SCH_2; 4.52, part of the AB-quartet, J=18 Hz, 1H, SCH_2; 5.29, d, J=5 Hz, 1H, ß-lactam; 5.78, d, J=55 Hz, 2H, CH_2F; 5.94, dd, J=5 Hz and 8 Hz, 1H, ß-lactam; 8.28, b, 2H, NH_2; 8.63, s, 1H, CH=N; 9.84, d, J=8 Hz, 1H, NH

17 1.40 – 1.70, m, 4H, CCH_2; 1.88 – 2.30, m, 4H, CCH_2; 2.88, d, 3H, NCH_3; 3.08, b, 9H, NCH_3; 3.20 – 3.80, m, 3H, 2H from NCH and 1H from SCH_2; 4.51, part of the AB-quartet, J=18 Hz, 1H, SCH_2; 5.29, d, J=5 Hz, 1H, ß-lactam; 5.78, d, J=55 Hz, 2H, CH_2F; 5.95, dd J=5 Hz and 8 Hz, 1H, ß-lactam; 8.30, b, 2H, NH_2; 8.68, s, 1H, CH=N; 9.84, d, J=8 Hz, 1H, NH

18 1.10 – 2.22, m, 8H, CCH_2; 2.90, d, 3H, NCH_3; 3.08 – 3.32, m, 1H, NCH; 3.40 – 3.80, m, 2H, 1H from NCH and 1H from SCH_2; 3.54, part of the AB-quartet, J=18 Hz, 1H, SCH_2; 5.30, d, J=5 Hz, 1H, ß-lactam; 5.77, d, J=55 Hz, 2H, CH_2F; 5.96, dd, J=5 Hz and 8 Hz, 1H, ß-lactam; 8.52, s, 1H, CH=N; 9.86, d, J=8 Hz, 1H, NH

19 1.30 – 1.75, m, 8H, CCH_2; 1.80 – 2.20, m, 8H, CCH_2; 2.80 – 3.20, m, 2H, NCH; 3.28, s, 3H, NCH_3; 3.40 – 3.75, m, 3H, 2H from NCH and 1H from SCH_2; 4.20, part of the AB-quartet, J=18 Hz, 1H, SCH_2; 5.15, d, J=5 Hz, 1H, ß-lactam; 5.76, dd, J=5 Hz and 8 Hz, 1H, ß-lactam; 5.79, d, J=55 Hz, 2H, CH_2F; 8.09, s, 1H, CH=N; 9.84, d, J=8 Hz, 1H, NH

20 1.02 – 2.20, m, 8H, CCH_2; 2.90 – 3.18, m, 1H, NCH; 3.32, s, 3H, NCH_3; 3.42 – 3.78, m, 2H, 1H from NCH and 1H from SCH_2; 3.55, part of the AB-quartet, J=18 Hz, 1H, SCH_2; 5.28, d, J=5 Hz, 1H, ß-lactam; 5.78, d, J=55 Hz, 2H, CH_2F; 5.94, dd, J=5 Hz and 8 Hz, 1H, ß-lactam; 8.12, s, 1H, CH=N; 9.82, d, J=8 Hz, 1H, NH

21 1.10 – 2.22, m, 8H, CCH_2; 3.00 – 3.18, m, 1H, NCH; 3.35, b, 3H, NCH_3; 3.45 – 3.82, m, 1.5H, 1H from SCH_2 and 0.5H from NCH; 4.10 – 4.30, m, 0.5H, NCH; 3.54, part of the AB-quartet, J=18 Hz, 0.5H, SCH_2; 3.62, part of the AB-quartet, J=18 Hz, 0.5H, SCH_2; 5.12 – 5.22, m, 1H, ß-lactam; 5.70 – 5.85, m, 1H, ß-lactam; 5.78, d, J=5 Hz, 2H, CH_2F; 8.10, b, 1H, CH=N; 9.77, d, J=8 Hz, 1H, NH

22 1.08 – 1.62, m, 4H, CCH_2; 1.70 – 2.25, m, 4H, CCH_2; 2.90 – 3.20, m, 1H, NCH; 3.32, b, 3H, NCH_3; 3.42 – 3.82, m, 2H, 1H from NCH and 1H from SCH_2; 4.45 – 4.70, m, 1H, SCH_2; 5.10 – 5.28, m, 1H, ß-lactam; 5.65 – 5.90, m, 1H, ß-lactam; 5.78, d, J=55 Hz, 2H, CH_2F; 8.10, b, 1H, CH=N; 9.85, d, J=8 Hz, 1H, NH

23 1.30 – 2.00, m, 7H, CCH_2; 2.10 – 2.30, m, 1H, CCH_2; 3.25 – 3.62, m, 5H, 3H from NCH_3, 1H from NCH and 1H from SCH_2; 3.98 – 4.18, m, 1H, NCH; 4.53, part of the AB-quartet, J=18 Hz, 1H, SCH_2; 5.18, d, J=5 Hz, 1H, ß-lactam; 5.78, dd, J=5 Hz and 8 Hz, 1H, ß-lactam; 5.79, d, J=55 Hz, 2H, CH_2F; 8.11, s, 1H, CH=N; 9.75, d, J=8 Hz, 1H, NH

24 1.30 – 1.70, m, 10H, 4H from CCH_2 and 6H from CCH_3; 1.82 – 2.12, m, 4H, CCH_2; 2.88 – 3.12, m, 1H, NCH; 3.29, s, 3H, NCH_3; 3.42 – 3.70, m, 2H, 1H from NCH and 1H from SCH_2; 4.48, part of the AB-quartet, J=18 Hz, 1H, SCH_2; 5.32, d, J=5 Hz, 1H, ß-lactam; 5.98, dd, J=5 Hz and 8Hz, 1H, ß-lactam; 7.06, s, 1H, CH thiazol; 8.11, s, 1H, CH=N; 9.68, d, J=8 Hz, 1H, NH

25 1.22 – 1.70, m, 4H, CCH_2; 1.82 – 2.18, m, 4H, CCH_2; 2.88 – 3.18, m, 1H, NCH; 3.45 – 3.80, m, 4H, 3H from NCH_3 and 1H from SCH_2; 3.96 – 4.28, m, 1H, NCH; 4.48, part of the AB-quartet, J=18 Hz, 1H, SCH_2; 5.25, d, J=5 Hz, 1H, ß-lactam; 5.78, d, J=55 Hz, 2H, CH_2F; 5.96, dd, J=5 Hz and 8 Hz, 1H, ß-lactam; 8.02, s, 1H, CH=N; 9.86, d, J=8 Hz, 1H, NH

26 1.30 – 1.60, m, 4H, CCH_2; 1.70 – 2.05, m, 4H, CCH_2; 2.80 – 3.05, m, 1H, NCH; 3.18, s, 3H, NCH_3; 3.38 – 3.68, m, 2H, 1H from NCH and 1H from SCH_2; 4.48, part of the AB-quartet, J=18 Hz, 1H, SCH_2; 5.22, d, J=5 Hz, 1H, ß-lactam; 5.76, d, J=55 Hz, 2H, CH_2F; 5.92, dd, J=5 Hz and 8Hz, 1H, ß-lactam; 7.85, s, 1H, CH=N; 9.82, d, J=8 Hz, 1H, NH

27 1.10 – 1.65, m, 4H, CCH_2; 1.72 – 2.25, m, 4H, CCH_2; 2.88 – 3.18, m, 1H, NCH; 3.32, s, 3H, NCH_3; 3.42 – 3.80, m, 2H, 1H from NCH and 1H from SCH_2; 4.54, part of the AB-quartet, J=18 Hz, 1H, SCH_2; 5.17, d, J=5 Hz, 1H, ß-lactam; 5.77, dd, J=5 Hz and 8 Hz, 1H, ß-lactam; 5.78, d, J=55 Hz, 2H, CH_2F; 8.10, s, 1H, CH=N; 9.85, d, J=5 Hz, 1H, NH

28 1.28 – 1.68, m, 4H, CCH_2; 1.88 – 2.15, m, 4H, CCH_2; 2.72 – 3.08, m, 4H, 3H from NCH_3 and 1H from NCH; 3.28, s, 3H, NCH_3; 3.40 – 3.72, m, 2H, 1H from NCH and 1H from SCH_2; 4.25, part of the AB-quartet, J=18 Hz, 1H, SCH_2; 5.27, d, J=5 Hz, 1H, ß-lactam; 5.78, d, J=55 Hz, 2H, CH_2F; 5.94, dd, J=5 Hz and 8 Hz, 1H, ß-lactam; 8.06, s, 1H, CH=N; 9.85, d, J=8 Hz, 1H, NH

29 (500 MHz, $CDCl_3/CH_3OD$)
0.82 - 0.88, m, 2H, CCH_2; 1.32 – 2.14, m, 10H, CCH_2; 2.68 – 2.82, m, 2H, NCH; 3.52 – 3.72, m, 2H, 1H from SCH_2 and 1H from NCH; 4.12, part of the AB-quartet, J=18 Hz, 1H, SCH_2; 5.15, d, J=5 Hz, 1H, ß-lactam; 5.78, d, J=55 Hz, 2H, CH_2F; 5.96, d, J=5 Hz, 1H, ß-lactam; 8.65, s, 1H, CH=N

30 1.10 – 1.68, m, 4H, CCH_2; 1.72 – 2.00, m, 7H, 4H from CCH_2 and 3H from CH_3; 3.32, s, 3H, NCH_3; 3.40 – 3.70, m, 3H, 2H from NCH and 1H from SCH_2; 4.56, part of the AB-quartet, J=18 Hz, 1H, SCH_2; 5.27, d, J=5 Hz, 1H, ß-lactam; 5.78, d, J=55 Hz, 2H, CH_2F; 5.94, dd, J=5 Hz and 8 Hz, 1H, ß-lactam; 8.09, s, 1H, CH=N; 9.85, d, J=8 Hz, 1H, NH

31 1.32 – 1.72, m, 4H, CCH_2; 1.80 – 2.12, m, 4H, CCH_2; 3.33, s, 3H, NCH_3; 3.40 – 3.90, m, 3H, 2H from NCH and 1H from SCH_2; 4.59, part of the AB-quartet, J=18 Hz, 1H, SCH_2; 5.28, d, J=5 Hz, 1H, ß-lactam; 5.79, d, J=55 Hz, 2H, CH_2F; 5.95, dd, J=5 Hz and 8 Hz, 1H, ß-lactam; 7.32 – 7.58, m, 3H, aromatic-H; 7.70 – 7.90, m, 2H, aromatic-H; 8.10, s, 1H, CH=N; 9.86, d, J=8 Hz, 1H, NH

32 1.25 – 1.70, m, 4H, CCH_2; 1.75 –2.08, m, 4H, CCH_2; 2.18, s, 3H, CH_3; 3.30, s, 3H, NCH_3; 3.48 – 3.80, m, 3H, 2H from NCH and 1H from SCH_2; 4.54, part of the AB-quartet, J=18 Hz, 1H, SCH_2; 5.28, d, J=5 Hz, 1H, ß-lactam; 5.79, d, J=55 Hz, 2H, CH_2F; 5.96, dd, J=5 Hz and 8 Hz, 1H, ß-lactam; 7.08 – 7.60, m, 4H, aromatic-H; 8.08, s, 1H, CH=N; 9.86, d, J=8 Hz, 1H, NH

33 1.28 – 1.68, m, 4H, CCH_2; 1.75 – 2.02, m, 4H, CCH_2; 3.31, s, 3H, NCH_3; 3.48 – 3.75, m, 3H, 2H from NCH and 1H from SCH_2; 4.20, part of the AB-quartet, J=18 Hz, 1H, SCH_2; 4.50, s, 2H, NCH_2; 5.11, d, J=5 Hz, 1H, ß-lactam; 5.66, dd, J=5 Hz and 8 Hz,

1H, ß-lactam; 5.78, d, J=55 Hz, 2H, CH_2F; 6.82 – 7.02, m, 3H, aromatic-H; 7.22 – 7.40, m, 2H, aromatic-H; 8.08, s, 1H, CH=N; 9.75, d, J=8 Hz, 1H, NH

34 1.15 – 1.55, m, 4H, CCH_2; 1.58 – 1.90, m, 4H, CCH_2; 2.05, s, 3H, CH_3; 2.75 – 3.05, m, 1H, NCH; 3.25, s, 3H, NCH_3; 3.32 – 3.68, m, 2H, 1H from NCH and 1H from SCH_2; 4.50, part of the AB-quartet, J=18 Hz, 1H, SCH_2; 5.28, d, J=5 Hz, 1H, ß-lactam; 5.77, d, J=55 Hz, 2H, CH_2F; 5.96, dd, J=5 Hz and 8 Hz, 1H, ß-lactam; 7.65 – 7.90, m, 4H, aromatic-H; 8.05, s, 1H, CH=N; 9.84, d, J=8 Hz, 1H, NH

35 1.15 – 1.68, m, 4H, CCH_2; 1.72 – 2.05, m, 4H, CCH_2; 3.25 – 3.72, m, 8H, 3H from NCH_3, 2H from NCH, 2H from NCH_2 and 1H from SCH_2; 4.20, part of the AB-quartet, J=18 Hz, 1H, SCH_2; 5.12, d, J=5 Hz, 1H, ß-lactam; 5.70, dd, J=5 Hz and 8 Hz, 1H, ß-lactam; 5.76, d, J=55 Hz, 2H, CH_2F; 6.80 – 7.00, m, 2H, thiophenyl-H; 7.30 – 7.40, m, 1H, thiophenyl-H; 8.08, s, 1H, CH=N; 9.76, d, J=8 Hz, 1H, NH

36 1.30 – 1.78, m, 4H, CCH_2; 1.88 – 2.12, m, 4H, CCH_2; 2.64, s, 3H, SCH_3; 2.90 – 3.18, m, 1H, NCH; 3.52 – 3.72, m, 4H, 3H from NCH_3 and 1H from SCH_2; 3.88 – 4.12, m, 1H, NCH; 4.32, part of the AB-quartet, J=18 Hz, 1H, SCH_2; 5.30, d, J=5 Hz, 1H, ß-lactam; 5.77, d, J=55 Hz, 2H, CH_2F; 5.98, dd, J=5 Hz and 8 Hz, 1H, ß-lactam; 8.38, s, 1H, CH=N; 9.88, d, J=8 Hz, 1H, NH

A1 1.10 – 1.60, m, 4H, CCH_2; 1.72 – 2.12, m, 4H, CCH_2; 2.75 – 3.08, m, 1H, NCH; 3.30 – 3.60, m, 1H, NCH; 8.30, b, 3H, NH

A2 1.08 – 2.20, m, 8H, CCH_2; 3.00 – 3.28, m, 1H, NCH; 3.60 – 3.88, m, 1H, NCH; 7.72, b, 2H, NH; 8.48, b, 3H, NH

A3 1.00 – 2.20, m, 8H, CCH_2; 2.78, s, 3H, NCH_3; 3.05 – 3.32, m, 1H, NCH; 3.60 – 3.85, m, 1H, NCH; 8.50, b, 3H, NH

A4 1.25 – 1.65, m, 4H, CCH_2; 1.70 – 2.20, m, 4H, CCH_2; 2.70 – 3.08, m, 4H, 3H from NCH_3 and 1H from NCH; 3.35 – 3.65, m, 1H, NCH; 8.35, b, 3H, NH

A5 1.00 – 2.20, m, 8H, CCH_2; 2.78, s, 3H, NCH_3; 3.05 – 3.32, m, 1H, NCH; 3.60 – 3.85, m, 1H, NCH; 8.50, b, 3H, NH

B1 1.12 – 1.55, m, 4H, CCH_2; 1.75 – 1.98, m, 4H, CCH_2; 2.30, b, 6H, NCH_3; 2.70, s, 3H, NCH_3; 3.20 – 3.80, m, 2H, NCH

B2 (D_2O) 1.22 – 1.70, m, 4H, CCH_2; 1.90 – 2.28, m, 4H, CCH_2; 2.70, b, 6H, NCH_3; 2.95 – 3.45, m, 2H, NCH

B3 1.10 – 1.88, 6H, CCH_2; 1.90 – 2.18, m, 2H, CCH_2; 2.37, s, 3H, NCH_3; 2.76, s, 3H, NCH_3; 2.83, s, 3H, NCH_3; 3.32 – 3.62, m, 2H, NCH

C1 1.40 – 1.70, m, 4H, CCH_2; 1.82 – 2.30, m, 4H, CCH_2; 2.80, s, 3H, NCH_3; 3.05, b, 9H, NCH_3; 3.30 – 3.50, m, 1H, NCH; 3.60 – 3.80, m, 1H, NCH

C2 1.18 – 1.70, m, 4H, CCH_2; 1.88 – 2.30, m, 4H, CCH_2; 3.05, b, 9H, NCH_3; 3.20 – 3.68, m, 2H, NCH

D1 (D_2O) 1.20 – 1.60, m, 8H, CCH_2; 1.80 – 2.18, m, 8H, CCH_2; 2.95 – 3.20, 5H, 3H from NCH_3 and 2H from NCH; 3.22 – 3.48, m, 2H, NCH

D1 1.25 – 1.60, m, 4H, CCH_2; 1.82 – 2.18, m, 4H, CCH_2; 3.00 – 3.20, 4H, 3H from NCH_3 and 1H from NCH; 3.22 – 3.45, m, 1H, NCH

D2 - D5, D8

1.10 – 2.25, m, 8H, CCH_2; 2.88 – 3.12, m, 1H, NCH; 3.20, s, 3H, NCH_3; 3.52 – 3.85, m, 1H, NCH; 7.75, b, 2H, NH; 8.40, b, 3H, NH

D6 (D_2O) 1.25 – 1.60, m, 4H, CCH_2; 1.82 – 2.18, m, 4H, CCH_2; 3.00 – 3.20, 4H, 3H from NCH_3 and 1H from NCH; 3.22 – 3.45, m, 1H, NCH

D7 (D_2O) 1.50 – 1.90, m, 8H, CCH_2; 3.09, s, 3H, NCH_3; 3.20 – 3.40, m, 1H, NCH; 3.50 – 3.68, m, 1H, NCH

E1 1.35 – 1.72, m, 4H, CCH_2; 1.82 – 2.30, m, 4H, CCH_2; 3.05, b, 9H, NCH_3; 3.20, s, 1H, NCH_3; 3.30 – 3.72, m, 2H, NCH; 7.45, d, J=4 Hz, 1H, NH; 7.74, b, 2H, NH

H1 1.30 – 1.65, m, 4H, CCH_2; 1.78 – 2.15, m, 4H, CCH_2; 2.70 – 3.00, m, 4H, 3H from NCH_3 and 1H from NCH; 3.14, s, 3H, NCH_3; 3.22 – 3.55, m, 1H, NCH; 8.19, b, 3H, NH

H2 (DMSO-d_6/D_2O) 1.20 – 1.50, m, 4H, CCH_2; 1.78 – 2.02, m, 4H, CCH_2; 2.80 – 3.10, m, 1H, NCH; 3.40, s, 3H, NCH_3; 3.80 – 4.05, m, 1H, NCH

H3 1.00 – 1.92, m, 17H, 9H from CCH_3 and 8H from CCH_2; 2.56, s, 3H, SCH_3; 3.00 – 3.25, m, 1H, NCH; 3.51, s, 3H, NCH_3; 3.68 – 3.92, m, 1H, NCH

G1 1.10 – 1.40, m, 4H, CCH_2; 1.50 – 1.80, m, 4H, CCH_2; 2.65 – 2.90, m, 1H, NCH; 3.10, s, 3H, NCH_3; 3.20 – 3.50, m, 1H, NCH; 6.85, d, J=4 Hz, 2H, aromatic-H; 7.52, d, J=4 Hz, 2H, aromatic-H

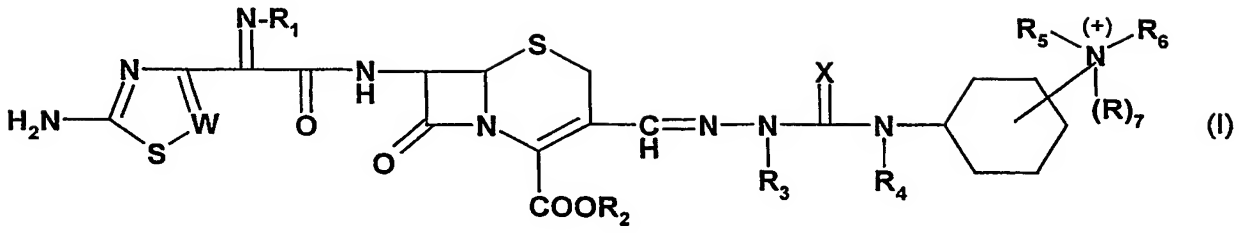
I1 1.00 – 1.50, m, 13H, 9H from CCH_3 and 4H from CCH_2; 1.60 – 1.90, m, 4H, CCH_2; 3.08, s, 3H, NCH_3; 3.25 – 3.80, m, 2H, NCH

F1 (D_2O) 0.88 – 1.75, m, 6H, 4H from CCH_2 and 3H from CCH_3; 1.80 – 2.35, m, 4H, CCH_2; 2.90 – 3.70, m, 4H, 2H from NCH_2 and 2H from NCH

F2 (D_2O) 1.20 – 1.65, m, 4H, CCH_2; 1.80 – 2.22, m, 4H, CCH_2; 3.00 – 3.20, m, 1H, NCH; 3.22 – 3.52, m, 1H, NCH; 3.88 – 4.20, m, 2H, NCH_2; 4.98 – 5.40, m, 2H, $C=CH_2$; 5.55 – 5.88, m, 1H, CH=C

Patent claims:

1. A compound of formula



(I)

wherein

W is CH or N,

R_1 is hydrogen, hydroxy, (C_{1-6})alkoxy, halo(C_{1-6})alkoxy, hydroxycarbonyl(C_{1-6})alkoxy or (C_{1-6})alkyloxycarbonyl(C_{1-6})alkoxy,

R_2 is hydrogen or an ester moiety,

R_3 is hydrogen, (C_{1-6})alkyl, allyl or cyclo(C_{1-6})alkyl,

R_4 is hydrogen or methyl,

R_5, R_6 and R_7 are independently from each other hydrogen, (C_{1-6})alkyl, (C_{1-6})alkylcarbonyl, arylcarbonyl, aryl(C_{1-6})alkycarbonyl, heteroaryl(C_{1-6})alkylcarbonyl, (C_{1-6})alkylsulfonyl, arylsulfonyl or aryl(C_{1-6})alkylsulfonyl, or R_7 is missing and N^+-$R_5R_6R_7$ or N-R_5R_6 can be in o, m or p position, and

X is N-R_8 , O, S, O-R_8 or S-R_8 wherein R_8 is hydrogen, (C_{1-6})alkyl, cyclo(C_{1-6})alkyl or aminocyclo(C_{1-6})alkyl.

2. A compound according to claim 1 of formula I wherein

W is CH or N,

R_1 is hydroxy, methoxy, fluoromethoxy, hydroxycarbonylmethoxy or hydroxycarbonylisopropyloxy,

R_2 is hydrogen,

R_3 is hydrogen, methyl, allyl or cyclopropyl,

R_4 is hydrogen or methyl,

R_5, R_6 and R_7 are independently from each other hydrogen, methyl, phenylcarbonyl, aryl substituted by acetyloxo, phenyloxyacetyl, phenylsulfonyl substituted by amino or acetylamino, 1-thiophene-2-yl-acetyl or cyclohexyl substituted by amino, or R_7 is missing

and N^{+}-$R_5R_6R_7$ or N-R_5R_6 can be in o, m or p position, and
X is NH, NCH_3, O, S, S-(C_{1-6})alkyl, amino substituted aminocyclohexyl.

3. A pharmaceutical composition comprising a compound according to any one of claims 1 to 2 in association with at least one pharmaceutical carrier or diluent.

4. Use of a compound according to any one of claims 1 to 3 as a pharmaceutical.

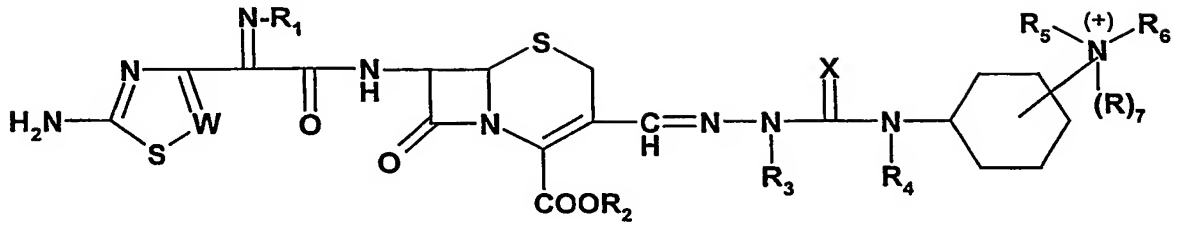
5. Use according to claim 4 in the treatment of microbial diseases.

6. A method of treatment of microbial diseases which comprises administering to a subject in need of such treatment an effective amount of a compound according to any one of claims 1 to 4.

IL/20-Sep-2002

Abstract:

A compound of formula



(I)

wherein the substituents have various meanings, useful as a pharmaceutical.

IL/20-Sep-2002